# A I D S TREATMENT N E W S

**Issue Number 399**
**March 26, 2004**

Published 12 times a year by
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AIDS Treatment News
1233 Locust St., 5th floor
Philadelphia, PA 19107


## Contents

# AIDS Treatment News

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**Statement of Purpose:**

*AIDS Treatment News* reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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with two antiretroviral regimens that failed last year. Several possible causes for the failure had been proposed. Now it appears that the problem was too low a genetic barrier to HIV developing certain resistance mutations.

**Retroviruses Conference: Summaries for Physicians.....**

This collection of CME trainings for physicians gives an in-depth review of major reports from the Retroviruses conference (February 8-11 in San Francisco), focusing on what HIV physicians need to know.

**Medicines for the World: A Way Forward.....**

For poor and middle-income countries we should negotiate large sales involving many countries, with all the interests at the table. Large deals and public consensus could make it viable for companies to develop treatments for diseases affecting poor regions.

## Clinton Foundation Negotiates $140/Year HIV Treatment, But U.S. Won't Buy

by John S. James

On April 6 the Clinton Foundation, along with the World Bank, UNICEF, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria announced that it could negotiate prices as low as $140 per year for triple-combination treatment -- part of an effort to help over 100 countries get low-cost HIV treatment and diagnostic tests. The final price for poor-country governments will depend on several conditions, and will not include the cost of getting the drugs registered (approved) in each country. For more information see the April 6 report by the Kaiser Family Foundation.(1)

But by March 2004 the Bush Administration had decided that the U.S.

would not pay for these generic medications, at least not now. President Bush himself had supported use of the less-expensive drugs in his 2003 State of the Union address, which called for spending $15 billion over 5 years in 14 African and Caribbean countries. But a year later, the Administration reversed course and said that recipients of the U.S. PEPFAR program (the President's Emergency Plan for AIDS Relief, the nominally $15 billion program) could not use the money to buy generic antiretrovirals, because these drugs had not approved by the FDA or other stringent regulatory agency accepted by the U.S.

The FDA has not evaluated these generics because they are patented in the U.S. and could not legally be registered for sale or sold here. Instead, they were approved by the World Health Organization's well-regarded WHO Prequalification Project, based on bioequivalence data submitted by the companies -- the same way generic medicines are approved for U.S. use by the FDA. The WHO set up this program to help poor countries identify and buy safe and effective but low-cost antiretrovirals of assured quality. It relies on Canadian, European, and Australian drug regulators to assist in its assessments and inspections.

The U.S. organized a March 29-30, 2004 conference in Gaborone, Botswana to try to build international consensus that the generic versions, already in use by tens of thousands of patients in many countries, were not reliable and needed additional testing -- which would have undermined the WHO Prequalification Project and the low-cost medicines it had approved. Instead, the meeting strengthened the international consensus that the Bush administration was blocking generics on behalf of the proprietary pharmaceutical companies, which do not want widespread use in poor countries of generic copies of medicines that they have patented in rich countries (and sell there for 20 times the price or more). The EMEA, the European equivalent of the U.S. FDA, boycotted the Botswana conference by refusing to send any experts, after participating in an earlier planning meeting. Nevertheless the WHO, UNAIDS, and SADC (the Southern African Development Community) will be under great pressure to ultimately sign a "consensus" document acceptable to the Bush Administration.

A March 26, 2004 letter from Congressman Henry Waxman to President Bush(2) summarized problems with the U.S. position. For example, it noted that before the Botswana meeting the U.S. circulated a proposal ("Scientific and Technical Principles for Fixed-Dose Combination Products") that appears to require major clinical trials for approving generic fixed-dose combinations for HIV, trials not required for similar approvals in the U.S. And some of the trials requested might not pass ethical review.

A new draft of the document should be posted in mid-April for public comment.(3) It is likely to call for different ways to re-test and re-approve generic medicines already accepted by the World Health Organization and in widespread use in the field.

The issue received extensive press coverage (see references 4, 5, 6, and 7 below, for a partial list), especially on March 25, 26, and 27, 2004.

AIDS and public-health experts are very concerned that blocking the use of generics would:

* Greatly limit the number of people that can be treated, by requiring the use of drugs that cost three to four times more. (The main factor limiting how many people get treatment will probably be lack of money.)

* Stop the use of fixed-dose combinations (FDCs), in which all antiretrovirals drugs needed by most patients when they begin treatment are combined into a single pill to be taken once in the morning and once

at night. The proprietary pharmaceutical companies do not make these FDCs, because different companies have patents on different components, and today's pharmaceutical companies do not work together well with their competitors. (The generic drug manufacturers, not restricted by the patents, created the fixed-dose combinations at the request of Doctors Without Borders and the World Health Organization.) Making patients take separate pills will certainly increase chances for error, and almost certainly lead to splitting of regimens for sharing the different pills within families, resulting in treatment failure for everyone and the development of resistant viruses.

* A critical need now is for fixed-dose pediatric antiretroviral formulations for children. Dr. Eric Goemaere of MSF (Doctors Without Borders) in South Africa recently described the current problem:

"How can you tell the grandmother that she needs to give -- for example a very specific dosage of nevirapine, a very specific amount of another drug and do exactly what we ask with them? She now has three different syrups in three different bottles with three different labels and she is supposed play the nurse and administer three different amounts from each. Fixed combinations would definitely be easier, and allow us to extend treatment to rural areas as well."(8)

The brand-name companies probably will not make fixed-dose pediatric regimens because of the patent problems. Generic companies will be slower to develop these formulations if the U.S. refuses to pay for them and otherwise discourages their use.

* Health experts face tremendous challenges in quickly getting treatment to millions of people who have never had access to modern medicine before -- and who will die of AIDS in the next few years if they do not receive antiretrovirals. The U.S. demand for a second, more complicated regimen will cause serious administrative problems and public confusion.

## The Biggest Problem

The central problem here is that with millions of lives at stake, people are not on the same page in fighting the epidemic. Pharmaceutical companies, with immense influence on the world's only superpower, have no commercial incentive to save lives in poor countries. But they have strong incentives to avoid any examples or precedents there that might reduce their ability to charge high prices in the U.S., or otherwise threaten their business model (a business model that must change anyway, for a variety of reasons). The result is that the U.S. government does not allow AIDS treatment programs in poor countries to work as well as they could.

Imagine the difference if "big pharma" would help lobby rich governments to fund treatment and control of epidemics around the world, instead of impeding treatment because another industry's products are most likely to be used.

In our comment "Medicines for the World: A Way Forward" in this issue, we show that this situation is not inevitable, and propose incentives for a different business model that could make for-profit treatment development work better in an inequitable world.

## References

1. Kaiser Family Foundation, "Drug Access: Clinton Foundation, Global Fund, World Bank, UNICEF Extend Low-Cost Generic AIDS Drug Prices to More Than 100 Countries," at:
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=23059

2. Congressman's Waxman's letter of March 26 to President Bush is available at:

http://lists.essential.org/pipermail/ip-health/2004-March/006151.html

3. The new draft document should be posted in mid-April, 2004, at a U.S. Department of Health and Human Services site:
http://www.globalhealth.gov/fdc.shtml

4. *Wall Street Journal*, March 25, "White House Gets Pressure on AIDS Plan; Activists, Drug Firms Duel Over Use of Funds for Generic Combination Drugs in Africa," by Sarah Lueck.

5. *New York Times*, March 26: "Plan to Battle AIDS Worldwide Is Falling Short," by Donald G. Mc.Neil Jr.

From this article: "Dr. Lembit Rago, who leads the W.H.O. assessments, said he used 'absolutely the same principles' as the Food and Drug Administration, and borrowed his inspectors from regulatory agencies in Canada, France, Germany, Sweden and Switzerland. As soon as his office approved the Indian pills, he said, 'a very cold wind began to blow from the U.S.'"

6. *Wall Street Journal*, March 26, "U.S. Lawmakers Urge Acceptance of WHO-Approved AIDS Drugs," from Dow Jones newswires.

7. *Washington Post*, March 27: "Bush's AIDS Program Balks at Foreign Generics," by Stephen Brown.

8. The complete transcript of the March 25, 2004 MSF (Doctors Without Borders) teleconference is at:
http://www.doctorswithoutborders.org/publications/other/pepfar_teleconference_03-25-2004.shtml

# Atherosclerosis Risk Increased with HIV; Treatment Effects Unclear

by John S. James

An important study by cardiologists, endocrinologists, and HIV physicians found more atherosclerosis in persons with HIV, and much faster progression, than in the general population.(1) The measurement used in this study -- increasing thickness of the carotid artery, determined non-invasively by ultrasound examination -- is known to be a predictor of strokes and heart attacks in other populations. But this study could not tell how much of the increased risk is due to HIV itself, and how much is due to metabolic abnormalities caused by protease inhibitors or other HAART treatment in some patients.(2)

Age, LDL cholesterol, and smoking (cigarette pack-years) were strong

predictors of atherosclerosis in the 148 persons with HIV who were studied; Latino race and high blood pressure were weaker predictors. Other risks like diabetes would not have shown up in this study because of the small number of volunteers affected. When matched controls were added to the analysis, HIV infection itself was a strong predictor of greater atherosclerosis, independent of other factors.

The authors gave some practical clinical suggestions at the end of the article: "Although randomized trials have not been done to demonstrate that treatment of risk factors reduces events in HIV-infected patients, it seems reasonable to extrapolate from other populations and to recommend aggressive control of risk factors. Smoking is particularly important because of its high prevalence. Hypertension should be treated. LDL cholesterol should be reduced to low levels, and hypertriglyceridemia should be controlled. If lipids are difficult to control, antiretroviral medication that may be contributing to lipid elevation should be reviewed and changed to medication with fewer lipid effects. Until further data are available, treating to the National Cholesterol Education Panel guidelines(3) for patients with established vascular disease or diabetes seems prudent."

The researchers are from San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco. The volunteers were mostly recruited from the University of California, San Francisco Study of the Consequences of the Protease Inhibitor Era (SCOPE) study.

### References

(1) PY Hsue, JC Lo, A Franklin, AF Bolger, JN Martin, SG Deeks, and DD Waters. Progression of Atherosclerosis as Assessed by Carotid Intima-Media Thickness in Patients With HIV Infection. *Circulation.* 2004; volume 109, pages 1603-1608, April 6 (published online before print, March 15). The abstract is free at http://www.circulationaha.org - but the full article costs $15 online for nonsubscribers.

(2) Another recent study looked at triglyceride and cholesterol changes associated with different antiretrovirals, in a major analysis of data from over 7,000 HIV patients in 11 previously established cohorts. Some of its findings will be useful for particular patients, but overall it is hard to interpret this article. Reuters Health published a summary; you can find it on the AIDSMEDS site, at:
http://www.aidsmeds.com/news/20040323clin001.html.

Here is the reference for the original article:

E Fontas, F van Leth, CA Sabin, and others. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: Are different antiretroviral drugs associated with different lipid profiles? *Journal of Infectious Diseases.* March 15, 2004; volume 189, pages 1056-1074.

(3) Information on the National Cholesterol Education Program is available at:
http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

## Atazanavir (Reyataz): New Recommendations If Combined with Tenofovir (Viread) -- and Warning on Viagra, Cialis, and Levitra

On March 19, 2004 the FDA notified the public of new prescribing information and precautions for atazanavir (brand name

Reyataz), if taken in combination with tenofovir (Viread) -- and warned of risks with Viagra or similar drugs.

If atazanavir is taken with tenofovir, the blood level of atazanavir is decreased. Therefore it is now recommended that a small dose of ritonavir be taken in addition, to raise the blood level of atazanavir to compensate. All three drugs are taken together once per day, with food.

Also, Reyataz increases the blood level of Viread, which could increase its side effects. As a precaution, patients combining the drugs should be monitored for tenofovir side effects.

The new Patient Information flyer also warns that if atazanavir is combined with Viagra, Cialis, or Levitra, it could increase the risk of serious side effects of those drugs. Patients are advised not to combine atazanavir with any of these drugs unless their doctor tells them it is OK.

For more information see the new prescribing information for atazanavir, which will be posted at http://www.reyataz.com (we did not find it on the site on April 14). Also see the Patient Information flyer, which may be posted at the end of the prescribing information.

# Abacavir Hypersensitivity Reaction Predicted by Genetic Test

About 5% of patients have a potentially serious reaction to abacavir (Ziagen), and must discontinue the drug and never use it again. Now researchers in Australia have reported new data showing that testing for certain genes can accurately predict who will have this reaction.

In their cohort of 248 patients, 18 of whom had the reaction, a genetic test for HLA-B*5701 alone would reduced the risk of abacavir hypersensitivity from 8% to 0.4% -- but would result in about 1.6% of their patients being inappropriately denied the drug. Adding a second genetic test would reduce these false positive from 1.5% to 0.4%. These figures will vary by racial groups, or by geographic regions within the same race, because of the different genetic inheritance of different populations.

The researchers presented their findings at the Retroviruses conference (February 8-11, 2004 in San Francisco), and published a full report on March 15. They are now using the testing in their clinical practice, to avoid giving abacavir to patients who are likely to react to it. This testing is not in general use, however.

Incidentally, having HLA-B*5701 is probably an advantage overall, because it is associated with slower HIV progression.

### For More Information

For an overview of presentations on this subject at the Retroviruses conference, see "Pharmacogenetics Predict Abacavir (Ziagen) Hypersensitivity" by Deborah Mitchell, published March 1, 2004 on the HIV and Hepatitis site:
http://www.hivandhepatitis.com/recent/nrtis/030102d.html

Original paper: Martin AM, Nolan D, Gaudieri S and others. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proceedings of the National Academy of Sciences, USA.* Published online before print, March 15, 2004. Free abstract, and link to full text, available at:
http://www.pnas.org/cgi/content/abstract/0307067101v1

# Update on Sculptra (New-Fill) Hearing

On March 25 an FDA advisory panel unanimously recommended that the FDA approve Sculptra (New-Fill) for facial wasting caused by HIV treatment or HIV. They also want restrictions so that it will not be used widely for less urgent purposes like filling wrinkles, unless the

company (Dermik Laboratories) comes back with data to support that use. The committee was not happy with the limited amount of data available, but was moved by HIV patients' testimony about their need for the treatment.

## Lessons from Two "Triple Nuke" Failures (New Training Module)

Last year two three-drug regimens that had once seemed reasonable (tenofovir + 3TC + abacavir; also tenofovir + 3TC +ddI) were found to work very badly; these combinations must never be used alone as antiretroviral treatment, because they fail in most patients and cause serious drug resistance. There were different theories of why these three-drug regimens failed, but now it is widely believed that the main problem is that they did not provide a high enough genetic barrier to the development of two viral mutations, K65R and M184V, which led to resistance to the drugs.

(The picture is different for the four-drug combination AZT + 3TC + abacavir + tenofovir, which is showing good results even though it contains one of the problematic combinations within it. The AZT helps prevent the K65R and M184V resistance pattern from developing.)

On March 31 Clinical Care Options published a half-hour training module for physicians (but available to anyone) explaining this situation, and what has been learned from it. This module, titled "Lessons Learned: The Perils of Extrapolation - Combination NRTI Use" will be available for one year at:
http://www.clinicaloptions.com/hiv
Under "Treatment Update," click "Lessons Learned." Note: free one-time registration is required to use this site.

## Retroviruses Conference: Summaries for Physicians

The results most important to physicians from the 11th Conference on Retroviruses and Opportunistic Infections (February 8-11, 2004) have been presented as in CME (Continuing Medical Education) training modules by Clinical Care Options. Credit is offered for physicians and registered nurses.

The five major topics are:
* Management of Treatment-Naive Patients;
* Resistance, Salvage Therapy, & Treatment Strategies;
* Metabolic Complications and Lipodystrophy;
* Pharmacology and Adverse Drug Effects; and
* Hepatitis Coinfection and Opportunistic Infections.

Each of these five CME modules is a discussion among experts, on an average of about 12 sub-topics each. Links from the expert discussion to "capsule summaries" show key results in a standardized table format. The advantage of these summaries is that they present the data in a way that all the experts accept, so discussion can focus on the key issues instead of on presenting the numbers.

Most patients will need help understanding these training modules, which were written for physicians. They could benefit from a discussion group, led by someone who knows the material. The leader could explain the information that is important to everyone in the group, and answer questions as necessary. Since each topic is generally independent and does not require knowledge of the others, patients could come to the meetings that focused on what they needed to know, and skip the others.

AIDS groups could contribute by organizing such discussions. Most of the advance preparation has already been done, since the material has been selected and organized by leading experts.

One way to run such a group is the "journal club" format, where students each